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APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
10/078,677	02/21/2002	Didier Branellec	03804.0111-01	5864

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EXAMINER
PRIEBE, SCOTT DAVID

ART UNIT	PAPER NUMBER
1632	5

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
10/078,677	Branellec et al.
Examiner	**Art Unit**
Scott D. Priebe, Ph.D.	1632

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) X Responsive to communication(s) filed on *Feb 21, 2002*.

2a) This action is **FINAL**. 2b) X This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) X Claim(s) *36-44* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) X Claim(s) *36-44* is/are rejected.

7) Claim(s) _____ is/are objected to.

8) Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) X The drawing(s) filed on *Feb 21, 2002* is/are a) X accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) X Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) X All b) Some* c) None of:

1. Certified copies of the priority documents have been received.
2. X Certified copies of the priority documents have been received in Application No. *08/633,769*.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) The translation of the foreign language provisional application has been received.

15) X Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)	Notice of References Cited (PTO-892)	4)	Interview Summary (PTO-413) Paper No(s).
2)	Notice of Draftsperson's Patent Drawing Review (PTO-948)	5)	Notice of Informal Patent Application (PTO-152)
3) X	Information Disclosure Statement(s) (PTO-1449) Paper No(s). 4	6)	Other:

DETAILED ACTION

The preliminary amendment filed with the application has been entered. Claims 1-35 have been cancelled and claims 36-44 have been added. The first sentence of the specification has been amended by the Examiner to update the status of application 08/633,769 which has issued as a patent by replacing "allowed" with --U.S. Pat. No. 6,410,011--.

Specification

The abstract of the disclosure is objected to because of the use of legal phraseology. Applicant is reminded of the proper language and format for an abstract of the disclosure. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. Correction is required. See MPEP § 608.01(b).

Claim Objections

Claim 44 is objected to because of the following informalities: "emthod" is misspelled, and should be replaced with --method--. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 36, 37, and 39-44 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a human or canine replication-defective adenovirus whose genome comprises a left and right inverted and terminal repeat (ITR), an encapsidation signal, and a suicide gene operably linked to a promoter controlling expression in cells infected by the adenovirus, does not reasonably provide enablement for adenovirus in general, adenovirus with a genome lacking one or both ITRs and/or an encapsidation signal, therapeutic genes in general, and genes, including a suicide gene, not operably linked to a suitable promoter. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The specification discloses replication defective adenovirus vectors comprising a suicide gene under control of a promoter operable in cells infected by the adenovirus for use in methods of inhibiting smooth muscle cell proliferation. Claims 39, 41, 43 and 44 broadly recite any therapeutic gene. However, the specification does not teach any therapeutic gene other than a suicide gene, much less another type of therapeutic gene which upon expression would act to inhibit a decrease in luminal diameter of an atheromatous blood vessel. Thus the teachings of the specification are not commensurate in scope with the claimed subject matter. The specification must teach those of skill in the art how to make and how to use the invention as broadly as it is claimed. *In re Goodman*, 29 USPQ2d 2013 (CA FC 1994), citing *In re Vaeck*, 20 USPQ2d 1445

(CA FC 1991). The claims should be limited to a suicide gene in view of the lack of guidance in the specification for any other type of therapeutic gene.

Given that claims 38, 40, and 42 appear to limit the broader invention by requiring an adenoviral encapsidation signal and left and right ITRs, the broader invention embraces embodiments where the genome of the adenovirus lacks one or more of the encapsidation signal, left ITR or right ITR. The specification does not describe how one could make an adenovirus comprising a suicide gene, or any other gene, without the suicide gene being present in a genome that can be packaged into an adenoviral capsid. As taught in Grable et al. (J. Virol. 66 (2): 723-731, 1992), it is not possible to package an adenoviral genome that lacks a packaging sequence. As taught in Hay et al. (J. Mol. Biol. 175: 493-510, 1984) it is not possible for an adenoviral genome to replicate without both a left and right ITR. Without such replication, there would be nothing to package. Thus, embodiments, embraced by the broader claims, wherein one or more of these essential sequences are missing are inoperative. Claims 36, 39 and 41 should be amended to clearly indicate that the genome of the adenovirus comprises left and right ITRs and an encapsidation signal.

Given that claims 38, 40 and 42 appear to limit the broader invention by requiring the suicide gene be operably linked to a promoter, the broader invention must embrace embodiments where the suicide gene (or therapeutic gene) is not operably linked to a promoter. The claimed invention, as described in the specification (e.g. page 3), is based upon the activity of the product of the suicide gene (see page 3 of the specification, for example). In order for the suicide gene to

effect cell killing, it must be expressed in target cells to produce a gene product. This cannot occur if the suicide gene is not operably linked to a promoter, and specifically a promoter that is active in the transfected cells of the blood vessel. The specification does not describe how one could use an adenovirus comprising a suicide gene without the suicide gene being operably linked to a promoter, and specifically a promoter that mediates expression of the suicide gene in transfected cells of the blood vessel, e.g. vascular smooth muscle cells. Such embodiments would be inoperative for the stated utility of killing transfected cells (and neighboring cells). The base claims should be amended to clearly indicate that the suicide gene is or will be expressed in transfected cells of the blood vessel. e.g. by recitation of a promoter operably linked to the suicide gene, which directs expression of the suicide gene in blood vessel cells.

Claims 39-44 are broadly directed to any adenovirus. The specification discloses the hypothetical use of any and all animal adenoviruses for practice in the inventions. However, the specification fails to disclose the transfection of any and all animal adenoviruses into human cells and achieving expression therein and is not enabling for the broad scope of the claims for adenoviruses of "animal origin" and infection of, and expression in, human cells . Case law teaches (*Ex parte Forman*, 230 USPQ 546, 547 (PTO Bd. App. Int. 1986) that "the disclosure of a patent application must enable practice of the invention claimed without undue experimentation", wherein factors involved in the determination of undue experimentation were deemed to include "the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention,

the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims".

The specification fails to disclose the nucleotide sequences or restriction maps of other "animal" adenoviruses, or any other structural or genetic characteristics of animal adenoviruses in general, or guidance in the construction and propagation of animal adenovirueses in general. Therefore, the specification is not enabling for the genetic manipulation encompassing the insertion of a suicide gene or any other therapeutic gene into other "animal" adenoviruses. The specification merely alludes to the availability of adenoviruses of "animal origin" and fails to disclose methods by which the insertion, or genetic manipulation of their viral DNA, of therapeutic genes may be accomplished. Mere mention that adenoviruses of other animal origin exist does not enable the development and subsequent use of vectors made therefrom. The vast majority of adenoviruses of animals other than human or canine were poorly characterized when the instant invention was made, and almost none at the genetic level required to determine which parts of the genome could be altered to produce a vector and to develop the necessary packaging cells required to produce the recombinant adenovirus required for the method. No evidence has been presented that the specification provides such information or that it was available in the prior art sufficient to practice the method as it is broadly claimed.

It is well known in the art that at least one adenovirus from another animal differs in both nucleotide sequence and genomic organization from the well characterized human adenoviruses. For example, Both (WO 97/06826, published 27 February 1997) discloses (pages 2 and 3) that

the genome sequence and arrangement of OAV287 (ovine adenovirus 287) is different from all known human, animal and avian adenoviruses, including the canine adenovirus, the bovine adenovirus, and the avian CELO adenovirus isolate. Both discloses that the OAV is serotypically distinct, not neutralized by serum human Ad5 and that this is consistent with the distinctive amino acid sequences in the hexon, penton and fiber antigens. Both discloses that there are also other major differences in the capsid proteins of OAV compared with other known adenoviruses: that OAV lacks capsid protein homologues V and IX but contains at least two other structural proteins; that due to the low nucleotide sequence homology between OAV and other adenoviruses there is little chance of recombination between OAV and another adenovirus during co-infection in the host to form an infectious recombinant virus. Restriction maps represent preliminary basic knowledge of an otherwise uncharacterized genome, allowing one of skill to identify potential restriction sites for future insertion of human genes. The specification fails to disclose similar information, or whether the other adenoviruses have been cloned and therefore obtainable as a pure isolate, for the disclosed bovine, murine, porcine, avian and simian adenoviruses and the claimed canine adenoviruses. In view of the foregoing, at the time the claimed invention was made, it would have required undue experimentation by one of skill to make the invention as broadly claimed since the specification fails to disclose the nucleotide sequence, restriction map, restriction sites or other information indicating characteristics comparable to the human adenoviruses, necessary to enable one of skill to practice the invention as claimed. Therefore, the claims must be limited to human or canine adenovirus.

The specification fails to disclose that other "animal" adenoviruses can actually enter human cells. Both discloses that critical to the use of OAV vectors for human gene therapy is the question of whether OAV can actually enter human cells; that entry of human adenoviruses into human cells occurs via a two-step process involving specific amino acid sequences in the fiber and penton base proteins; that first the virus attaches to an unidentified (emphasis added)surface receptor via the trimeric fiber protein which protrudes from the surface of the virus and that the second step is an interaction between the v class of integrins and RGD tripeptide which forms part of the penton protein complex at the base of the fiber spike. Both discloses that the OAV fiber protein is small and has a completely different sequence to its human adenovirus homologues. The instant specification is not enabling for the use of any and all animal adenoviruses since the specification fails to disclose that other animal adenoviruses can enter human cells and then express the therapeutic gene within the cell. Although the specification discloses that the adenoviruses from a wide variety of species are available through the ATCC, a review of the pertinent pages in the ATCC catalog discloses that the bovine, avian, porcine, simian and murine adenoviruses claimed have restricted host ranges. The specification fails to disclose methods to alter or redirect the naturally occurring host range and fails to provide guidance as to which amino acid residues to alter to effect the change. In view of the teachings of Both that the receptor on the human cell is unidentified and since the specification fails to provide the nucleotide sequence or amino acid sequence of the fiber and penton base proteins of

each animal adenovirus, the specification does not provide guidance enabling one of skill to predict which viruses might be reasonably expected to gain entry.

The specification fails to disclose that human smooth muscle cells of vascular origin are infectable with adenoviruses of "animal origin". The specification fails to provide guidance to one of skill as to which cell lines would be infectable by which animal virus and it would require undue experimentation by one of skill to obtain infection of a human cell or tissue not naturally expressing the unidentified receptor. One of skill would not be able to predict which cells or tissues would be capable of being infected since the receptor involved in adenoviral entry is unidentified. Both discloses that OAV can, for example, infect a variety of, but not all, human cell lines.

For the reasons set forth above, the specification is not enabling for the scope of the invention as claimed with respect to the type of adenovirus. The claims must be limited to the human or canine adenoviral vector. In view of state of the art for adenoviral vectors, the known differences in adenoviral structure and sequences existing between species and in view of the lack of guidance and working examples in the specification, undue experimentation would have been required of one of skill to practice the invention in view of the broad scope of the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (e) the invention was described in-
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

Claim 39 is rejected under 35 U.S.C. 102(e) as being anticipated by French et al., US 6,290,949 B1.

French et al. discloses a hydrogel-coated balloon catheter wherein the hydrogel is impregnated with a replication deficient adenovirus comprising a therapeutic gene whose expression reduces neointimal thickening in arteries resulting from restenosis, i.e. inhibits the decrease in luminal diameter of the artery. Claims 5-6 are directed to the general method, col. 11 teaches the therapeutic genes, and col. 17, lines 58-60, teaches the use of hydrogel-coated balloon catheters with the adenovirus impregnating the hydrogel. This rejection would be overcome by limiting the claim to a suicide gene, which French does not teach.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior

art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 36-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ohno et al. (Science 265: 781-784, Aug. 5, 1994) in view of either Steg et al. (Circulation 88(4 pt. 2): I-660, 1993) or Steg et al. (Circulation 90: 1648-1656, Oct. 1994).

Ohno teaches a method for delivering a replication defective adenovirus comprising a left and right ITR, encapsidation signal, and suicide gene under control of a promoter functional in arterial vascular smooth muscle cells to arterial cells by instillation with a double-balloon catheter. The reference does not teach delivery of the adenovirus while contained in hydrogel impregnated with the adenovirus coated onto a balloon catheter.

However, Steg (1993) and Steg (1994) discloses a comparison of these two methods of delivering an adenovirus to arterial sooth muscle cells in a mammal, and concluded that delivery of an adenovirus using the hydrogel-coated balloon catheter was more efficient for transfection of smooth than using the double-balloon catheter, such as described in Ohno. Steg (1994) further points out an additional advantage of the hydrogel-coated balloon catheter that arterial dilatation of a target stenosis and adenoviral transfection may be performed by the same action, unlike the double-balloon catheter method which requires a separate dilatation step prior to transfection.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the hydrogel-coated balloon catheter, where the hydrogel is impregnated with the adenovirus, for the double-balloon catheter described in Ohno because Steg

(1993) and Steg (1994) taught that the former method of delivery was more efficient. Steg (1994) disclosed an additional advantage that the step of dilatating a target stenosis can be performed in the same operation as the adenovirus delivery, rather than requiring two steps as in the Ohno method. In order to practice the method of Ohno and either Steg (1993) or Steg (1994), one would have made both a pharmaceutical composition comprising hydrogel impregnated with the adenoviral vector of Ohno, and a balloon catheter coated with the composition.

The instant claims recite an intended use limitation that the products be used to inhibit the decrease in luminal diameter of an atheromatous artery following physical damage. The method of Ohno did not involve atheromatous arteries, however, the instant claims do not recite any limitation in the products themselves that would distinguish them from the prior art products that would be used in the method of Ohno in view of Steg (1993) or Steg (1994), i.e. the prior art products and the claimed products are the same products. Also, Applicant cannot rely upon the foreign priority papers to overcome the part of this rejection involving Steg (1994) because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg.*

Co., 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claim 42 is rejected under 35 U.S.C. 101 as claiming the same invention as that of claim 19 of prior U.S. Patent No. 6,410,011. This is a double patenting rejection.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 36-41, 43 and 44 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-24 of U.S. Patent No. 6,410,011. Although the conflicting claims are not identical, they are not patentably distinct from each other because the patented claims disclose a pharmaceutical composition and device which are embraced or identical to those instantly claimed and are directed to a method embraced by the instantly claimed method.

Certain papers related to this application may be submitted to Art Unit 1632 by facsimile transmission. The FAX numbers are (703) 308-4242 or (703) 305-3014 for any type of communication. In addition, FAX numbers for a computer server system using RightFAX are also available for communications before final rejection, (703) 872-9306, and for communications after final rejection, (703) 872-9307, which will generate a return receipt. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott D. Priebe whose telephone number is (703) 308-7310. The examiner can normally be reached on Monday through Friday from 8 AM to 4 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Scott D. Priebe

SCOTT D. PRIEBE, PH.D.
PRIMARY EXAMINER